46.(new) The method according to Claim 44 wherein the formulation is a liquid aqueous syrup or suspension.

47.(new) A method according to Claim 44 in which the bacterial infection is otitis media.

48.(new) A method according to Claim 44 in which the bacterial infection is an upper respiratory tract infection.

49.(new) A method according to Claim 44 in which the bacterial infection is a lower respiratory tract infection.

REMARKS

Claims 1 to 31 have been cancelled. Claims 32 to 49 have been added. Support for the claims lie in the specification in the originally filed claims, and on page 2, lines 19 to 26. No new matter is believed added.

An IDS and PTOL1449 form accompanies this response.

In the parent application USSN 08/945,365, the outstanding office action rejected the claims in that application, Claims 32, 34 to 46, 51 to 54, and 61 to 66, under 35 USC §103(a) as being unpatentable over the Rooke et al. patent, the WO 91/15197 ('197), the G.B. 2,005,538 patent, the Ruberto et al., the Feldman et al. the Jacobson et al. and the Arguedas et al. references of record, as well as the WO 93/00898 and the Frashini et al. references. Applicant would like to address these rejections herein as the claims are similar. Applicants respectfully traverse this rejection.

The present invention is directed to an improved treatment of a bacterial infection in a pediatric patient wherein the formulation is administered in a total daily dosage of 45 mg/kg/day of amoxycillin in combination with 6.4 mg/kg/day of clavulanate. In a further aspect, the present invention is also directed to an improved treatment of a bacterial infection in a pediatric patient wherein the formulation is administered in a total daily dosage of 25 mg/kg/day of amoxycillin in combination with 3.6 mg/kg/day of clavulanate.

This dosage regimen takes into account the needs of a pediatric patient, and as the specification clearly demonstrates, provides for a dosage regimen which is as safe and effective as the previously known three times a day regimen at 40/10mg/kg/day (for more severe infections) and 20/5mg/kg/day (for less severe infections), but more

importantly, and unexpectedly were able to achieve this efficacy with a twice daily dosing schedule, and with reduced side effects.

The cited references are all earlier publications or patents, which reflect what was the actual marketed formulations at the time, i.e. a 2:1 or 4:1 weight ratio of components for tablet formulations and a 4:1 weight ratio for suspension formulations. These references do no do not address the issues of improved or enhanced efficacy in a twice daily dosage regimen, nor the impact of moving to a higher amoxycillin:clavulanate ratio on reduction of adverse side effects. The specification provides the necessary data and showings to overcome these rejections, including a clinical trial comparing the new 45/6.4 mg/kg day bid regimen with the existing 40/10 mg/kg tid regimen.

The WO 93/00898 publication, Reference BF, is a newly added reference by the Examiner. This application is directed to improving the stability of reconstituted powders by adding in a dicarboxylic acid/salt (e.g. succinic acid/sodium succinate). The ratios suggested include 12:1 to 1:1, preferably 8:1 to 1.5:1. There is no discussion of dosage (mg/kg/day) or frequency (bid vs. tid) of administration and is therefore silent on how the formulation should be used. Hence, the skilled artisan would utilize the existing state of the art.

In the WO 93/00898 publication is an example of a pediatric drops formulation (Example 2) The nominal ratio is 8:1. The skilled man would recognize this as based on an existing product, available in France, and one which used in a three times daily regimen, at a dose of 80/10 mg/kg/day. This is supported by reference CCD, in the accompanying IDS and PTOL 1449, for Augmentin in Vidal (the French equiv. of the Physicians Desk Reference or PDR). France has used 80/10 mg/kg/day tid for pediatric patients since about 1990. This formulation is of higher strength of amoxycillin than the 40/10 mg/kg/day (4:1) administered three times daily elsewhere in the world. Thus, there is no teaching or suggestion in this reference to direct the skilled artisan to use a lower amount 45/6.4 mg/kg/day with less frequency (twice daily).

As is discussed in Applicants earlier responses in the parent application 09/945,365, and incorporated herein by reference in their entirety, none of the remaining cited prior art discloses amoxycillin trihydrate and potassium clavulanate in a 45/6.4 mg/kg/day administered in a twice daily dosage regimen.

The Rooke et al. patent application, Reference AA, is directed to tablet/ unit dose formulations that include an edible desiccant. The wide weight range presented therein is typical of a large number of applications in this field. This application does not disclose pediatric formulations, nor the claimed twice daily dosing schedule.

The GB 2 005 538 (Crowley) patent, Reference BB, is a further "formulation invention" and is concerned with the specific use of amoxycillin as amoxycillin

trihydrate, in combination with potassium clavulanate, in the ratio of amoxycillin to clavulanate in the range 1:1 to 6:1. It does not describe the method of treatment of the present invention, nor a 7:1 formulation to be used in such.

The three cited publications describe clinical studies on a suspension product, which all use the existing 4:1 formulation, and again do not describe the use of a 7:1 product as claimed herein.

Ruberto et al. is a publication, Reference CA, which describes a clinical trial using a 4:1 formulation, at 40 mg/kg/day, for urinary tract infections, but with twice daily dosing, which at the time of the Ruberto clinical had an approved regimen of three times daily. This reference does not provide the skilled man with the necessary motivation to consider other formulations, (such as claimed herein) since the one used in the trial, a 40/10mg/kg/day formulation, appears to be clinically effective.

The Feldman et al. publication, Reference CB, describes a comparison between twice daily trimethoprim-sulfamethoxazole and twice daily amoxycillin/clavulanate (40 mg/kg/day) in otitis media and concludes that the trimethoprim-sulfamethoxazole is more effective and produces fewer side effects (see last sentence of the abstract) than the amoxycillin/clavulanate. This reference also discloses that more GI side effects were seen with the amoxycillin/clavulanate combination than the trimethoprim-sulfamethoxazole, and does not provide a solution to the issue or problems of administering an amoxycillin/clavulanate formulation in a twice daily regimen.

The Jacobsson et al. publication, Reference CC, describes another study comparing the original amoxycillin/clavulanate suspension given twice daily (at an average dosage of about 30 mg/kg/day) or three times daily (at an average dosage of mg/kg/day), in otitis media. Again, a regimen of a 45/6.4mg/kg/day formulation administered twice daily is not taught nor suggested by this reference. Indeed, the twice daily regimen is considered to be as effective as the three times daily regimen, providing no incentive to the skilled man to consider other dosages of amoxycillin and clavulanate.

Furthermore, both, Ruberto et al. and Jacobsson et al. note that their "new" twice daily regimens are associated with significantly more adverse effects than the corresponding three times daily original regimens with which they were being compared. This would surely act as a disincentive to the skilled man to further consider the use of a twice daily regimen. The prior art actually creates a problem without a solution, and teaches away from the invention claimed herein.

Applicants have solved that problem by providing for a 45/6.4 mg/kg/day formulation to be administered in a twice daily dosing regimen. This regimen is an unlikely switch not taught nor described by the prior art. In effect, this regimen

provides for a higher amount of daily dosage of amoxycillin (mg/kg/day) and a reduction in the daily dosage of clavulanic acid. Furthermore, Applicants showed that in order to provide equivalent clinical efficacy for a dosing interval of 12 hours rather than eight hours of the existing approved regimen, while the amount of amoxycillin given each time needed to be raised/increased, the amount of clavulanate could be held more or less constant. Thus, about 3.2mg/kg clavulanate was surprisingly as effective over 12 hours as over 8 hours.

It was not predictable that this would have the desired impact on adverse side effects while at the same time maintaining the efficacy of the formulation against beta-lactamase producing organisms, when the new dosage formulation was given in two equal amounts, every 12 hours. The reported studies had showed only that the higher levels of clavulanic acid were effective.

The rejection also includes the Arguedas et al. article, Reference CDB herein, but it is unclear if this is the previously cited abstract, or the complete article which was provided for in a citation in Applications response of 6 April 2001 in the parent application 08/945,365. Clarification is requested. The complete Arguedas et al. article, J. Antimicrob. Chemother., 27 (3) 311-8 (1991) is provided for herewith as reference CZ.

The Arguedas et al. reference discloses *S. pneumoniae* infections treated with an amoxycillin/ clavulanate formulation in a 2:1 ratio which is also outside the range of the claims herein. The Arguedas et al. reference also presents data (Table 1, page 314) which clearly demonstrates that amoxycillin appears to be more effective than amoxycillin/clavulanate in treating *S. pneumoniae* infections, (MIC 90% of 0.25 and 0.50, respectively). Therefore, the skilled man would have no incentive to use a combination of amoxycillin plus clavulanate to treat a *S. pneumoniae* infection when amoxycillin alone appears to be more effective.

Thus, none of the cited references describe a method of treatment according to the claims herein which take into account a safe and effective antibacterial formulation which results in reduced side effects, has a twice daily dosing regimen, and a formulation which contains a dosage amount calculated to deliver 45/10mg/kg/day of the active agents. All that the prior art shows is that a range of different ratios/amounts has been considered for tablet & suspension formulations, without regard to the dosage regimen for use thereof.

In light these remarks, Applicants respectfully request reconsideration and allowance of the claims herein.

Conclusion

Should the Examiner have any questions or wish to discuss any aspect of this case, the Examiner is encouraged to call the undersigned at the number below. If any additional fees or charges are required by this paper the Commissioner is hereby authorised to charge Deposit account 19-2570 accordingly.

Respectfully submitted,

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VERSION TO SHOW CHANGES MADE

Claims 1 to 31 have been cancelled.

Claims 32 to 49 have been added.